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Photodynamic Therapy in the Management of Metastatic Cutaneous Adenocarcinomas: Case Reports From Phase 1/2 Studies Using Tin Ethyl Etiopurpurin (SnET2)

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Background and Objectives: Photodynamic therapy (PDT) using a photoreactive purpurin, tin ethyl etiopurpurin (SnET2, Purlytin®, Miravant Medical Technologies, Santa Barbara, CA), was investigated as a treatment for cutaneous metastatic disease that had failed other treatment options.
Study Design/Materials and Methods: Three patients with biopsy-proven metastatic adenocarcinoma of the skin were treated with a single dose of the study drug. Twenty-four hours later, the patients were exposed to a laser light at 664 nm in multiple light fields. Patients were followed for 6 months for safety, efficacy, recurrence, and palliative response.
Results: After PDT with SnET2, complete response was observed in all 13 treated lesions in three patients, with no evidence of recurrence at any treated site at the 6-month follow-up. Two patients subsequently died of distant metastatic disease. One patient with local chest wall recurrence after mastectomy was disease-free 24 months after PDT.
Conclusions: PDT with SnET2 could be an effective treatment in locally advanced metastatic carcinoma of the skin.
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KEY WORDS: MeSH words; adenocarcinoma; photochemotherapy; photosensitizing agents

INTRODUCTION

Photodynamic therapy (PDT) is a relatively new therapeutic modality shown to be effective in the treatment of several types of cancer [1,2]. PDT utilizes photoreactive drugs, or photosensitizers, which are selectively retained by tumor cells and other hyperproliferating tissues [3,4]. In tissue, the photosensitizer alone will not cause damage to the cells [5], but when activated by exposure to specific wavelengths of light, several photochemical reactions occur, one of which is thought to be the production of singlet oxygen [6]. These excited oxygen species initiate a free radical chain reaction leading to vascular thrombosis, disruption of cellular organelles, and tumor necrosis [7–11]. The principal components needed for effective PDT therapy include a blood supply to deliver adequate concentrations of photosensitizer and oxygen to the target tissue and an effective delivery system to provide the activating light to the compound. Cellular death is accomplished at a subcellular level through the activation of pathways that produce toxic effects within the cell. These effects may include cell membrane disruption, lipoprotein breakdown, possible DNA disruption, and elevated free oxygen radical concentrations [12,13]. Photodynamic therapy allows patients to be treated on an outpatient basis and can be performed in a cost-effective manner.

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Tin ethyl etiopurpurin (SnET2, Purlytin®, Miravant Medical Technologies, Santa Barbara, CA) is one of a new generation of photosensitizing compounds that has shown encouraging preliminary results in Phase 1/2 studies in the treatment of primary cutaneous carcinomas and AIDS-related Kaposi's sarcoma (in preparation). SnET2 is a synthetic purpurin that is structurally similar to chlorophyll and can be activated by 664 nm visible red light. The longer activation wavelength of this photosensitizer provides an improved depth of penetration over the first generation compounds [14,15]. Also, it is these investigators' experience that the normal skin sensitivity generally associated with photodynamic therapy is both minimal and easily managed when using SnET2. This report describes three cases from a study to evaluate the effectiveness of PDT using SnET2 in the treatment of metastatic adenocarcinomas of the skin. The study was approved by the Institutional Review Board at the Albert Einstein Medical Center, and each patient provided written informed consent.

CASE REPORTS

Patient 1

A 63-year-old female presented with a pleomorphic cystic adenocarcinoma of the left submandibular gland that was initially diagnosed in 1979. Prior therapy consisted of initial surgical excision, chemotherapy, and radiation therapy that included external beam, implants, and hyperthermia. She had progressive metastatic disease to her lungs and local invasion of her mandible and left facial nerve. This local spread of a salivary gland adenocarcinoma was considered essentially identical to cutaneous metastasis and treated accordingly. The biopsy showed adenocarcinoma with no unusual histologic patterns. She also developed a progressive facial nerve palsy. Due to further ulceration of the lesion, and given her lack of conventional therapeutic options, she was referred for PDT therapy. She had not received chemotherapy or radiation therapy within 30 days prior to photodynamic therapy.

A complete metastatic workup was performed, including liver function studies, CBC, urinalysis, and chest X-ray. A single lesion was evaluated for depth, surface area, and location. Photographs were taken to assist in pre- and post-treatment evaluations (see Fig. 1). Surface area calculations included the diameter of the lesion plus 0.5 cm on all sides to provide adequate treatment of the tumor margins. The lesion was estimated to be no greater than 1 cm deep, as required by the study protocol.

The patient received an intravenous infusion of SnET2 in a lipid emulsion at 1.2 mg/kg body weight. Twenty-four hours after the administration of SnET2, the patient was pre-sedated with oral valium and the ulcerating lesion was treated within a single field of 10.5 cm^2 with 200 J/cm^2 of 664 nm (red visible) light from a dye laser module (Miravant Medical Technologies) that was powered by a 532 nm KTP laser (Laserscope, San Jose, CA) set to an output of 16 watts. The patient was discharged on the day of treatment.

The patient was followed on a weekly basis for 4 weeks following treatment and then monthly until 6 months post-treatment. The tumor was assessed at each visit for tumor effect and surrounding tissue effect, and the patient was questioned about pain reduction, quality of life, and adverse reactions to the therapy. After a transient episode of facial swelling, the patient developed a deep eschar over the lesion, with the surrounding area preserved and showing only moderate erythema. After 1 month, the patient's nerve palsy resolved and epithelialization of the area was noted. She was classified as a complete response (complete reduction of tumor) 3 months after therapy. Biopsy of the lesion site showed no evidence of disease. The patient died 1 year later of progressive metastatic disease.

Patient 2

A 64-year-old female presented with metastatic adenocarcinoma of her colon to her perianal and buttock area in 1992. The patient had a subsequent colostomy, chemotherapy with 5-FU leucovorin, and radiation therapy. She had continued cutaneous spread of her disease and developed intractable pain, resulting in her inability to sit or put pressure on the area of disease. The biopsy showed adenocarcinoma with no unusual histologic patterns. She had not received chemotherapy or radiation therapy within 30 days prior to photodynamic therapy.

A complete metastatic workup was performed, including liver function studies, CBC, urinalysis, and chest X-ray. The patient received an intravenous infusion of SnET2 in a lipid emulsion at 1.2 mg/kg body weight. Twenty-four hours later, the patient returned to the Ambulatory Care Center at Albert Einstein Medical Center for light treatment. Lesions in nine treatment fields in the perineal and perianal region were evaluated for depth, surface area, and location and were photographed for use in pre- and post-treatment evaluation. The nine light treatment fields covered a total surface area of 94 cm^2. All lesions selected for light treatment were estimated to be no greater than 1 cm deep, as specified by the study protocol. Light treatments were performed at power densities, not exceeding 150 mW/cm^2, set to deliver 200 J/cm^2 to each lesion. The patient was discharged after treatment and followed weekly for 4 weeks, then monthly until 6 months post-PDT. At 3 months post-therapy, the patient was free of pain and classified as a complete response. Multiple follow-up biopsies at 6 months showed no evidence of recurrence. The patient remained free of local disease and pain until her death from distant metastatic disease.

Fig. 1. Pre-treatment, immediate post-treatment, and follow-up evaluation of patient with a pleomorphic cystic adenocarcinoma of the left submandibular gland. **(Top)** Pre-treatment, metastatic cutaneous adenocarcinoma in area of mandible. **(Middle)** Post-treatment at 24 hours, showing selective response to tumor. **(Bottom)** Post-treatment at 12 weeks, biopsy negative for disease, re-epithelializing, healing by secondary intention.

Patient 3

A 62-year-old female was treated for stage I cancer of the right breast in June 1987, with a lumpectomy, node dissection, and radiation therapy. After local recurrence in 1989, she had a simple mastectomy with immediate reconstruction. In November 1994, she developed nodular densities at her mastectomy site that were biopsy-proven recurrent breast cancer. The biopsy showed adenocarcinoma with no unusual histologic patterns. At the time of evaluation for PDT, the patient had not received chemotherapy or radiation treatment within 30 days.

Pre-treatment preparation was performed, as described for Patient 1. The patient underwent PDT with SnET2 at three sites, with a total treatment area of 31.5 cm^2. At 1 week post-PDT, the three lesions had become necrotic (see Fig. 2) and were surgically debrided after 2 weeks. At 2 months she was observed to have a complete response and a 6-month biopsy showed no evidence of disease. She was followed for an additional 18 months (a total of 24 months post-PDT) without evidence of local recurrence.

DISCUSSION

Review of the above cases suggests that PDT with SnET2 could be an effective therapy for advanced cutaneous metastatic disease. The selective response seen in these patients may indicate that SnET2 exhibits the same preferential retention within tumor tissues as seen in other porphyrin compounds [5]. As illustrated in Figures 1 and 2, the extent of the therapeutic effect from photodynamic therapy is confined to the demarcation of the lesion, not the entire light field, providing evidence of selective absorption/retention of the photosensitizer in the tumor and not in normal tissue. Furthermore, previous radiation therapy to all PDT-treated areas had no significant impact on wound healing.

In addition to the eradication of local disease, all three patients had acceptable cosmetic results. Treated lesions healed with minimal scarring, and there was no residual erythema or evidence of surrounding skin damage. All of the patients reported an improved quality of life without significant interruptions in their daily routines, and one patient reported a dramatic decrease in pain posttreatment. All three patients expressed great satisfaction with the treatment and stated that they would not hesitate to undergo the therapy again, if needed.

Photodynamic therapy also offers increased efficiency in that the therapy can be done on an outpatient basis with reduced utilization of hospital resources. Moreover, the lack of significant side effects limits the need for additional medical intervention often seen in the more conventional treatment modalities.

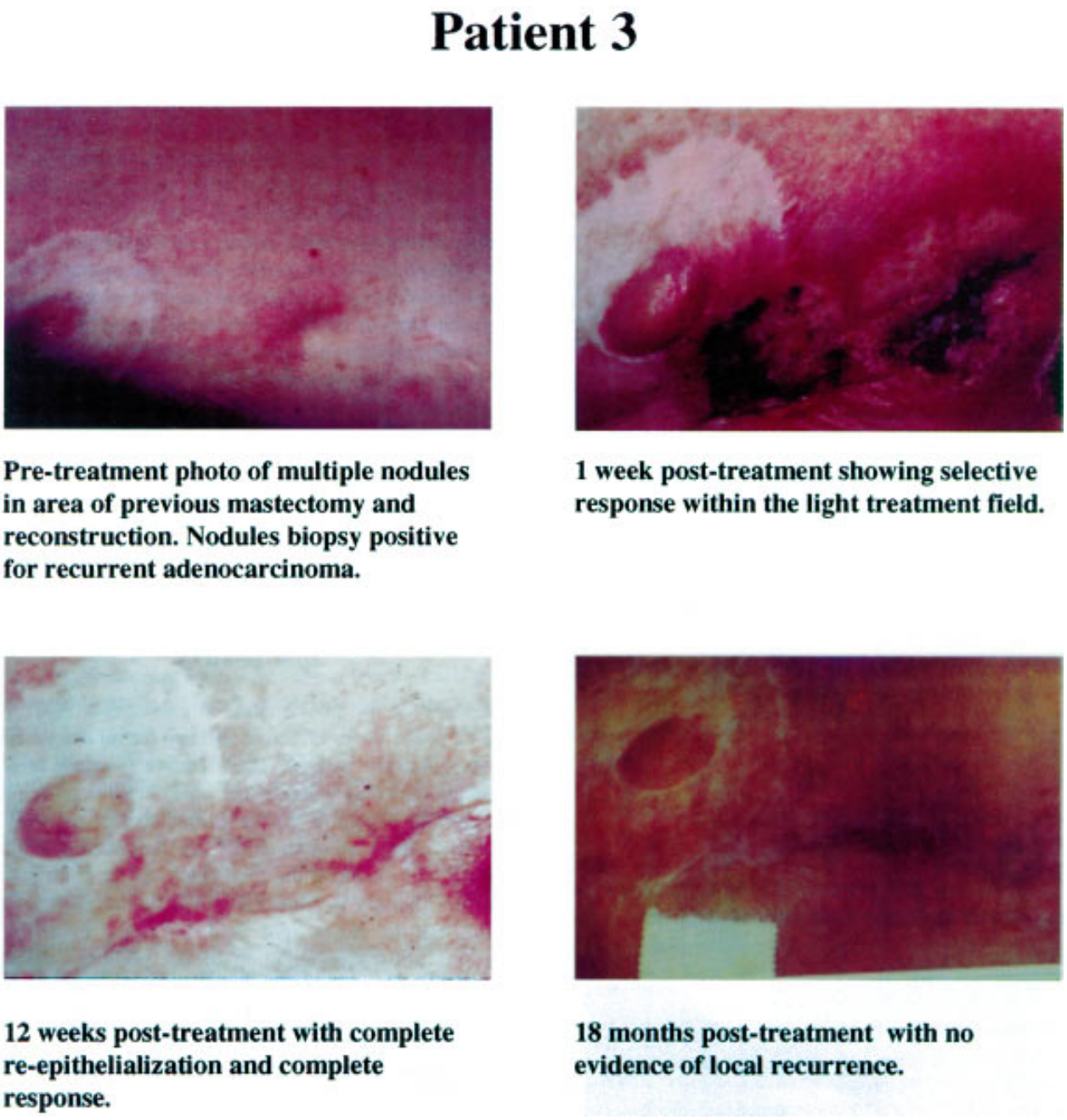

Fig. 2. Pre-treatment, post-treatment, and follow-up of local recurrent adenocarcinoma. **(Top left)** Pre-treatment photo of multiple nodules in area of previous mastectomy and reconstruction. Nodules biopsy positive for recurrent adenocarcinoma. **(Top right)** Post-treatment at 1 week, showing selective response within the light treatment field. **(Bottom left)** Post-treatment at 12 weeks, with complete re-epithelialization and complete response. **(Bottom right)** Post-treatment at 18 months, with no evidence of local recurrence.

CONCLUSION

This report demonstrates the potential of PDT with SnET2 as an excellent palliative modality in cases of metastatic cancer to the skin. PDT appears to have the unique ability to elicit direct cellular death in addition to thrombosis of the feeding blood vessels in the tumor tissue with a relative specificity that leaves the surrounding skin free of significant damage. Each patient presented had failed prior conventional therapies with rapid regrowth of their tumors; however, these patients tolerated photodynamic therapy with SnET2, showing minimal side effects and exhibiting excellent local control of the metastatic lesions. There is an ongoing Phase 2/3 trial to investigate these findings in a controlled setting and a larger patient population.

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